REMARKS

FORMAL MATTERS:

Claims 1-9 and 14-16 are withdrawn from consideration.

Claims 11 and 12 are amended for clarity. Support for these amendments is found in paragraphs 109 and 116.

New claims 17-29 are added. Support for these claims is found for example, in paragraph 60 (claims 17-20) 76 and 103 (claim 21), 104 and 116 (claim 22), 59 and 86 (claims 23-25), 87 (claim 26), 91 (claim 27), 75, 109 and 116(claims 28-29)

No new matter is added.

REJECTIONS UNDER §102

Claims 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson-Boaz, et al. This rejection is respectfully traversed.

To anticipate a claim, a prior art reference must disclose each and every limitation of the claimed invention, either expressly or inherently (MPEP 2131)

Claim 10 of the present invention recites "a pharmaceutical composition comprising a holin-modified bacteriophage and a *pharmaceutically acceptable carrier suitable for administration to a human subject*" (emphasis added). Dependent claim 12 requires the composition comprise "a mixture of *two or more different holin-modified bacteriophage*." Because claim 12 depends from claim 10, it includes all limitations of claim 10, and thus also requires a "*pharmaceutically acceptable carrier suitable for administration to a human subject*" (emphasis added).

In contrast, the Johnson-Boaz paper does not describe a preparation of bacteriophage in a pharmaceutically acceptable carrier suitable for administration to a human subject. Johnson-Boaz only describes two compositions containing holin-modified bacteriophage. The first composition described by Johnson-Boaz is a bacteriophage suspension which was prepared by obtaining phages from a culture plate. Specifically Johnson-Boaz states, "To make lysogens, phages were obtained by punching out single plaques from soft agar with a disposable Pasteur pipette, resuspending the material in 0.5ml of λdil,[1] and sterilizing by vortexing with a drop of $CHCl_3$" (Johnson-Boaz, page 502, col. 1, last

[1] The λdil buffer is described as containing "20mM Tris-HCl, pH 8.0, 10mM $MgCl_2$" (Johnson-Boaz, page 502, col. 1, second full paragraph).

paragraph). Not only does this preparation contain methyl chloride, but it also necessarily includes dead and/or lysed Gram negative bacteria, which served as the host for the phage.[2] As a result, this composition necessarily includes agar and agar components, as well as contaminating bacterial components such as lipopolysaccharides, which are known endotoxins. This composition would not be acceptable as, nor is it designed to be, a pharmaceutically acceptable carrier suitable for administration to a human.

The second composition described by Johnson-Boaz was one used to sequence the *S* gene of the phage. At page 502, col. 2, last paragraph, Johnson-Boaz describes the production of this composition as follows:

> **The primary λrj1 lysogen was induced and the resultant low-titre lysate plated on a MC4100 lawn. Two of the rare, tiny plaques which arose were punched out with a disposable pipette and resuspended by vortexing in 50 μl of water. PCR amplification of the *S* gene was done on this phage suspension, using Taq polymerase (Promega) essentially according to the manufacturer's instructions.**

Here, Johnson-Boaz simply suspended a mixture of the plaques, along with agar and contaminating bacterial hosts and bacterial host components, in water. Thus, not only does this composition contain components such as lipopolysaccharide as a contaminant, but it also likely contains live bacteria. This composition also fails to meet the requirement that *pharmaceutically acceptable carrier suitable for administration to a human subject* as recited in claim 10.

Johnson-Boaz thus fails to disclose a pharmaceutical composition comprising a holin-modified bacteriophage *and* a pharmaceutically acceptable carrier suitable for administration to a human subject, and thus fails to anticipate claims 10 and 12. Withdrawal of this rejection is respectfully requested.

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[2] Johnson-Boaz indicates the bacterial host used in the study is the strain MC4100, which is a laboratory strain of *Escherichia coli*, a Gram negative bacteria. See ATCC Product Description for MC4100, attached as Exhibit 1.

REJECTIONS UNDER §103(A)

Claims 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson-Boaz, et al. in view of Taylor et al. (U.S. Patent No. 2,851,006) and Clark. This rejection is respectfully traversed.

As set out in MPEP § 2142, a prima facie case of obviousness can only be made if three basic criteria are met:

1) There is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. 2) Second, there must be a reasonable expectation of success. 3) Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. All three criteria must be met. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established.

Claims 11 and 13 depend or ultimately depend from claim 10, and thus incorporate all limitations of claim 10. Claim 10 recites that the pharmaceutical composition comprises "*a pharmaceutically acceptable carrier suitable for administration to a human subject*". Accordingly, claims 11 and 13 also require a pharmaceutically acceptable carrier suitable for administration to a human subject.

As described above, Johnson-Boaz does not disclose a pharmaceutically acceptable carrier suitable for administration to a human subject, and thus does not disclose all the elements of the claimed invention. Neither of the disclosures of Taylor (U.S. Patent No. 2,851,006) or Clark provide this missing element.

Clark is generally directed to methods of preparing lyophilized bacteriophage preparations. To accomplish this, Clark discloses the method outlined below (column 1, paragraph 6 to column 2, paragraph 4). Comments as to the nature of the material at the various stages is provided as bulleted points below each step:

1) Propagate phage in broth "according to standard methods" ;
    - Phage propagation necessarily requires the phage be cultured with a compatible bacterial host in which the phage can replicate.
2) Centrifuge the broth containing the phage lysate;
    - At this stage, the broth contains the propagated phage, lysed bacteria (a "bacterial lysate"), and intact, whole bacteria (e.g., bacteria that may or

may not contain phage, but remain as intact cells at least some of which may remain viable)

3) Filter the centrifuged lysate through a Selas #03 porcelain filter;
   - The porcelain filter may be sufficient to remove at least some of the unlysed, intact cells, but would be insufficient to remove contaminants that result from lysis of the bacteria
4) Refrigerate the filtered lysate; and
5) Freeze-dry the lysate mixed with an equal volume of sterile, double-strength skim milk "as routinely practiced at the ATCC".

In alternate methods of preservation compared by Clark, Clark discloses that after step 3) above, the phage lysate is kept in broth alone; 50% glycerol is added to the broth, or the mixture is used to saturate a filter-paper, which is then dried over anhydrous calcium sulfate in a dessicator.. Clark also notes that "no special cleaning procedures were followed with the glass vials used" to store the lysate. Thus, at no stage of any of the methods disclosed in Clark does the disclosure provide a pharmaceutical composition comprising "*a pharmaceutically acceptable carrier suitable for administration to a human subject*". All methods involve a lysate which contains bacterial components.

Taylor, which discloses methods of treating fowl eggs (e.g. chicken eggs) with phage preparation, generally describes the following method for making the phage preparation (column 2 lines 45 to column 3 line 11):

1) Culture a composition of 50% raw sewage and 50% returned sludge with a desired target bacterium to generate a culture in which a bacteriophage have the desired bacterial host range is obtained;
2) Pass the culture through a filter to remove bacteria;
3) Repeat steps 1 and 2 until the liquid, described as a phage filtrate, is clear; and
   - The phage filtrate at this stage may be depleted of bacteria, but would still contain bacterial contaminants from lysed bacterial hosts.
4) Refrigerate the phage filtrate.

Taylor describes two ways to use the phage filtrate to treat eggs: 1) introduce the phage filtrate into the eggs by injection with a syringe (col 1, line 58 and col 3, lines 74-75 to col 4, line 1); or 2) place the place eggs in a liquid containing the phage filtrate and subject the eggs and liquid to a pressure differential to pass phage through pores of the egg.(col 1, lines 58-63 and col 3, lines 29-33 and col 4,

lines 14-23). Therefore, at no stage of the method disclosed in Taylor does the disclosure provide a pharmaceutical composition comprising "*a pharmaceutically acceptable carrier suitable for administration to a human subject*".

Accordingly neither Clark nor Taylor cure the deficiency of Johnson-Boaz in the failure to disclose or suggest a pharmaceutical composition comprising "*a pharmaceutically acceptable carrier suitable for administration to a human subject*". For at least this reason, the rejection of claims 11 and 13 should be withdrawn.

In addition, applicants note that any suggestion or motivation to modify Johnson-Boaz to arrive at the claimed invention must be independent of applicant's disclosure. As set out in MPEP §2142:

> To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

In this case, Johnson-Boaz not only fails to disclose or suggest a pharmaceutically acceptable carrier suitable for administration to a human subject as required by the pending claims, but fails to provide any teaching or suggestion that holin-modified bacteriophage would have any therapeutic benefit whatsoever. Accordingly there is no motivation to combine a holin-modified bacteriophage with a pharmaceutically acceptable carrier suitable for administration as required by claims 11 and 13. Neither Clark nor Taylor provide any suggestion or motivation to modify the holin-modified bacteriophage of Johnson-Boaz to provide for the pharmaceutical composition of claims 11 and 13.

Applicants respectfully submit that the present claims are not obvious under §103(a) over the combined disclosures of Johnson-Boaz, Clark and Taylor. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GANG-006.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: Feb 14, 2007

By: _____
Carol L. Francis, Ph.D.
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Enclosure(s): Exhibit 1: ATCC Product Description for MC4100

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